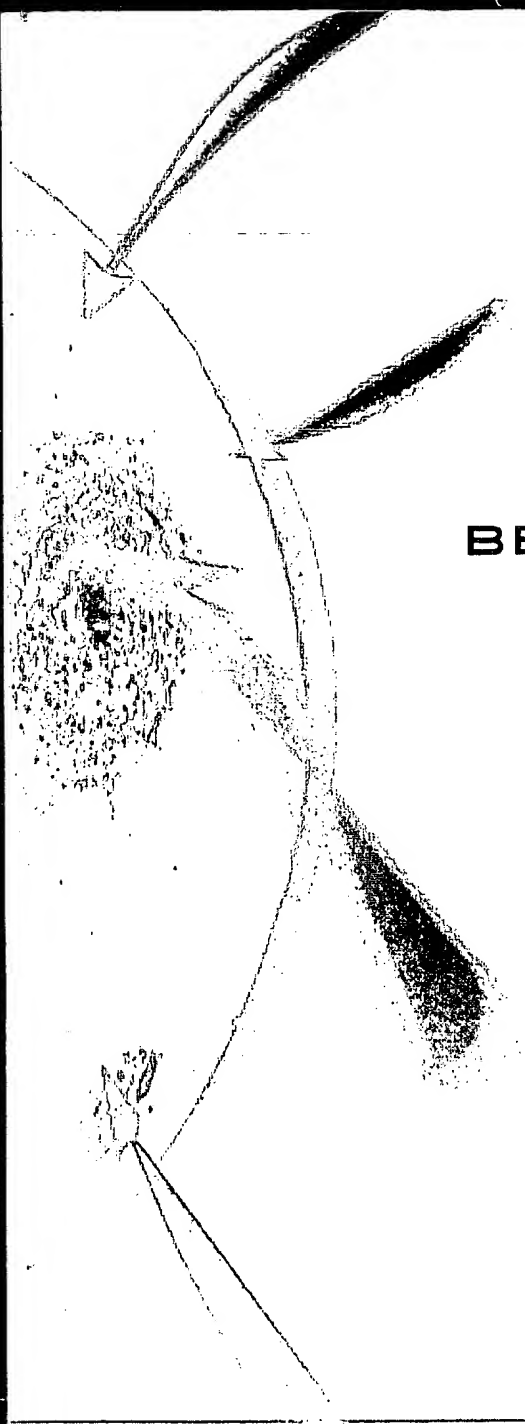
Exhibit A



BEYOND CHEMOTHERAPY

EMERGING TARGETED THERAPIES FOR THE TREATMENT OF CANCER

Proceedings

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Continuing Education Information

Target Audience

This continuing medical education program is intended for physicians and other health care professionals caring for patients with cancer.

Learning Objectives

Upon completion of this program, participants will be able to

- Describe the clinical development of epidermal growth factor receptor inhibitors, with a focus on their combined use with cytotoxic chemotherapy
- Discuss the clinical development of bcl-2 antisense technology in patients with advanced solid tumors
- Describe ongoing clinical and translational research utilizing farnesyl transferase inhibitors in aerodigestive tract cancers
- Identify therapeutic vaccine approaches that are currently being developed and evaluated in patients with cancer, with particular emphasis on the ALVAC canary pox vector

Sponsorship

This program is sponsored by Medical Education Resources.

Physician Accreditation

Medical Education Resources is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Medical Education Resources designates this continuing medical education activity for 2 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association. This CME activity was planned in accordance with ACCME essentials.

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Bcl-2 inhibition in the treatment of cancer: clinical studies with the Bcl-2 antisense oligonucleotide G3139

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Overview of Bcl-2

Bcl-2 and its related family of proteins are important regulators of apoptosis, or programmed cell death.[1] Apoptosis appears to be a result of a balance of pro- and anti-apoptosis proteins. Key components of this family of proteins are the anti-apoptotic protein Bcl-2 and the pro-apoptotic protein Bax. Irreparable cell damage, such as DNA damage caused by exposure to cytotoxic agents or ionizing radiation, can initiate signals that begin a cascade of events leading to apoptosis. These events are initiated by mitochondrial release of cytochrome C, which results in activation of Apaf-1 and subsequent activation of caspases, which in turn induce apoptosis (Figure 1, panel A).

In the presence of an abundance of Bcl-2, the apoptotic pathway is blocked and the cell remains viable (Figure 1, panel B). Increased expression of Bcl-2, resulting in altered apoptotic regulation and accumulation of cells, is considered to be an important component of the malignant process of many tumors. Depletion of Bcl-2 permits apoptosis, perhaps in part by freeing Bax (Figure 1, panel C). In the normal cell environment, dimerization of Bcl-2 with Bax or related proteins prevents Bcl-2 from interacting with the pathway. Because of its importance in apoptotic regulation, Bcl-2 is a reasonable target for the development of novel therapeutic agents, such as antisense oligonucleotides.

Overexpression of the Bcl-2 protein is a common feature in many solid and hematologic malignancies (Figure 2). Of importance, high levels of Bcl-2 can confer substantial resistance to multiple classes of chemotherapeutic agents.[1,2] While cells that overexpress Bcl-2 do incur drug-induced damage, the otherwise expected initiation of the apoptotic process does not occur.

Bcl-2 Antisense Therapy with G3139

G3139 (oblimersen, Genasense™) is an 18-mer phosphorothioate oligonucleotide that targets Bcl-2 mRNA. G3139 anneals to mRNA, inhibiting its translation, resulting in decreased Bcl-2 protein synthesis. Phosphorothioate is used to stabilize the antisense oligonucleotide, preventing breakdown by RNA-ases. Preclinical data in Bcl-2–overexpressing human tumor xenograft models indicate that treatment with G3139 alone can inhibit tumor formation in a dose-

Figure 1. The relationship between Bcl-2 and apoptosis. Model of the apoptotic pathway (panel A) and blockade of apoptosis by interactions with Bcl-2 (panel B). Prevention of Bcl-2 interaction, through mechanisms such as Bcl-2 protein dimerization with Bax or inhibition of Bcl-2 protein translation via antisense oligonucleotides, reestablishes the apoptotic process (panel C).

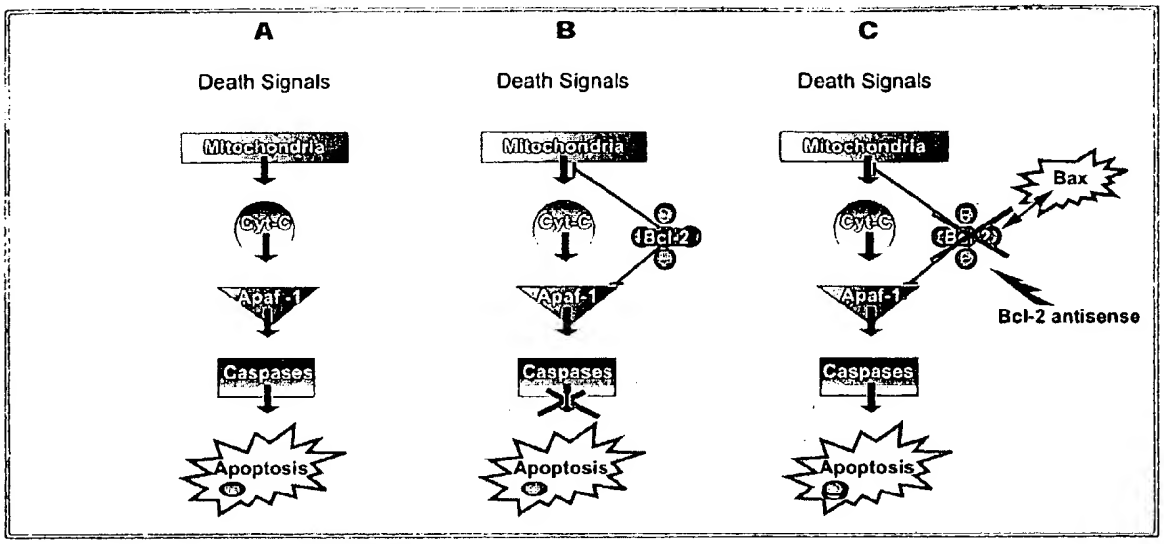
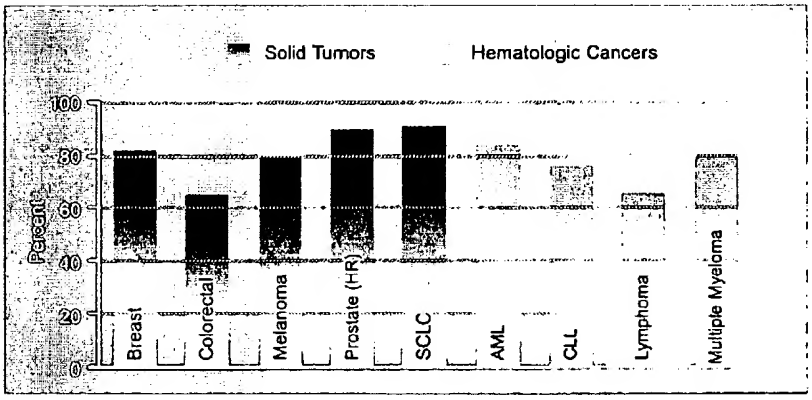


Figure 2. Overexpression of Bcl-2 in solid and hematologic malignancies



AML = acute myelogenous leukemia; CLL = chronic lymphocytic leukemia; HR = hormone-refractory; SCLC = small-cell lung cancer.

dependent manner.[3] Of particular interest, however, was the marked synergism observed when G3139 was administered in combination with subtherapeutic doses of docetaxel, paclitaxel, or cisplatin. In tumor xenograft–bearing animals so treated, complete tumor regression persisted for more than 5 months.

Several phase I studies with G3139 have recently been reported. Based on preclinical data, the very first trial of G3139 was conducted as a single-agent study in patients with non-Hodgkin's lymphoma (NHL).[4,5] In an effort to capi-

talize on potential synergistic effects, subsequent studies evaluated G3139 in combination with various chemotherapeutic agents (Table 1).[6-12] Current clinical trials are further evaluating the combination of G3139 with chemotherapy in a variety of tumor types (Table 2).

Single-Agent G3139

The initial phase I trial of G3139 evaluated single-agent therapy in patients with relapsed NHL.[4,5] G3139 was administered for 14 days by continuous subcutaneous infusion as a single course of therapy. Only 1 course of therapy was planned, but responding patients could be considered for a second treatment course. A total of 21 patients were enrolled, and G3139 doses were escalated from 4.6 to 195.8 mg/m^2/d. Three patients received 2 courses of therapy.

Although all patients experienced inflammation at the infusion site, no significant systemic toxicities were noted until doses exceeded 110.4 mg/m^2/d. The maximum tolerated dose was 147.2 mg/m^2/d (4 mg/kg/d), and dose-limiting toxicities included thrombocytopenia, hypotension, fever, and asthenia. Among the 21 patients, there were 1 complete response, 2 minor responses, and 9 patients with stable disease. Correlative laboratory studies of tumor cells derived from peripheral blood, bone marrow, or lymph nodes indicated down-regulation of Bcl-2 protein in 7 of 16 samples.

Table 1. Early clinical trials of G3139 and chemotherapy in solid tumors

Tumor Type	Regimen	No. of Evaluable Patients	Grade 3/4 Toxicities
Various[6]	G3139 1-4 mg/kg/d CIV x 21 d Docetaxel 35 mg/m^2 d 8, 15, 22 q 28 d	14	Grade 3 thrombocytopenia in 1 patient
Breast and other solid tumors[7]	G3139 5-9 mg/kg/d CIV d 1-5, 12-13, 19-20 Docetaxel 35 mg/m^2 d 6, 14, 21 q 28 d	9	Grade 3 thrombocytopenia in 1 patient
HRPC[8]	G3139 5-7 mg/kg/d CIV d 1-5 Docetaxel 60-100 mg/m^2 d 6 q 21 d	18	Grade 4 neutropenia in 4 patients
Melanoma[9,10]	G3139 0.6-6.5 mg/kg/d CIV x 14 d Dacarbazine 800-1000 mg/m^2 q 21 d or G3139 5-9 mg/kg/d CIV x 5 d Dacarbazine 1000 mg/m^2 q 21 d	24	Grade 3 lymphopenia in 5 patients; grade 3 transaminase elevations in 4 patients in 14 d schedule
Colorectal[11]	G3139 3-7 mg/kg/d CIV d 1-8 Irinotecan 280-350 mg/m^2 d 6 q 21 d	19	Grade 3/4 diarrhea, grade 3 nausea and vomiting, and grade 4 neutropenia were dose-limiting
SCLC[12]	G3139 3 mg/kg/d CIV d 1-8 Paclitaxel 150-175 mg/m^2 over 3 h d 6 q 21 d	12	Pruritic rash necessitating study discontinuation observed in 1 patient

CIV = continuous intravenous infusion; HRPC = hormone-refractory prostate cancer; SCLC = small-cell lung cancer.

Overall, treatment with G3139 was found to be tolerable, with antitumor activity suggested in patients with relapsed NHL. Laboratory evaluation confirmed that therapy with G3139 could affect downregulation of Bcl-2 production at clinically achievable concentrations.

G3139 and Docetaxel

Based on preclinical data suggesting synergy between G3139 and chemotherapy, several phase I clinical trials evaluating G3139 combination regimens in a variety of tumor types have been initiated (see Table 1).

At the Lombardi Cancer Center in Washington DC, we evaluated the combination of G3139 and docetaxel in patients with advanced breast cancer and other solid tumors. In the first part of this phase I trial, escalating doses of G3139 were administered by continuous infusion on days 1 through 21, with docetaxel 35 mg/m^2 administered on days 8, 15, and 22 of a 28-day cycle.[6] The study enrolled patients with advanced breast cancer or other solid tumors that overexpressed Bcl-2. Overexpression of Bcl-2 was defined as at least 20% of tumor cells positive for overexpression by immunohistochemical assay. Prior taxane exposure was allowed.

Fourteen patients were enrolled over 4 dose levels of G3139, ranging from 1 to 4 mg/kg/d. Overall, the dose-limiting factor in this trial was fatigue, with 1 grade 3 thrombocytopenia and several episodes of grade 1 and 2 transaminitis.

Table 2. Clinical studies with G3139

Tumor Type	Study Type	Regimen	Population
Melanoma	Phase III	DTIC ± G3139	First-line, advanced disease
Multiple myeloma	Phase III	Dexamethasone ± G3139	Relapsed or refractory disease
CLL	Phase III	Fludarabine/Cyclophosphamide ± G3139	Relapsed or refractory disease
CLL	Phase I/II	G3139	Relapsed or refractory disease
AML	Phase II	Gemtuzumab ozogamicin (Mylotarg™) + G3139	Relapsed disease, elderly patients
AML/ALL*	Phase I	Fludarabine/cytarabine + G3139	Relapsed or refractory disease
Prostate*	Phase I/II	Docetaxel + G3139	Androgen-independent disease
Breast and other solid tumors*	Phase I	Docetaxel + G3139	Advanced disease
NSCLC	Phase II	Docetaxel + G3139	Second-line, advanced disease
Colorectal*	Phase I/II	Irinotecan + G3139	Metastatic or recurrent disease
SCLC*	Phase I/II	Paclitaxel + G3139	Recurrent disease
SCLC	Phase I	Carboplatin, etoposide + G3139	First-line, extensive stage

*Accrual complete.

ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; NSCLC = non–small-cell lung cancer; SCLC = small-cell lung cancer.

Pharmacokinetics studies indicated that with G3139 doses of 3-4 mg/kg/d, resulting plasma concentrations exceeded those previously noted in vitro to produce synergy with docetaxel.

In the second part of the study, shorter infusion schedules of G3139 were evaluated in an effort to decrease the incidence of fatigue and transaminase elevations.[7] Patients received G3139 on days 1-5, 12, 13, 19, and 20, with docetaxel 35 mg/m^2 on days 6, 14, and 21 of a 28-day cycle. Nine patients received G3139 in dose cohorts of 5, 7, and 9 mg/kg/d. The majority of toxicities were grade 1 or 2, with only 1 patient experiencing grade 3 thrombocytopenia. Overall, 2 patients had partial responses and 4 patients had disease stabilization.

Bcl-2 expression in circulating peripheral blood leukocytes (PBLs) was monitored by 2 methods: flow cytometry and Western blot. Results have been mixed, but they suggest that PBL Bcl-2 levels decrease during treatment and return to baseline upon discontinuation. Data from other phase I clinical trials have shown some decrease in tumor cell Bcl-2 expression.

The combination of G3139 and docetaxel has also been evaluated in a phase I trial in patients with hormone-refractory prostate cancer.[8] G3139 was administered in escalating doses of 5-7 mg/kg/d for 5 days followed by docetaxel 60-100 mg/m^2, with cycles repeated every 21 days. In the preliminary report of 18 patients, dose-limiting toxicity had not been reached, although 4 patients experienced uncomplicated grade 4 neutropenia. Flow cytometric and Western blot analyses indicated marked downregulation of Bcl-2 protein expression in peripheral blood mononuclear cells. Durable prostate-specific antigen (PSA) responses were seen in 7 of 12 patients without prior taxane exposure, with a 50-fold reduction in PSA and major objective responses in the liver and viscera. These preliminary safety and efficacy data support further investigation of the combination.

G3139 and Dacarbazine

The combination of G3139 and dacarbazine has been evaluated in patients with malignant melanoma (see Table 1, page 14). Initially, G3139 was administered intravenously or subcutaneously at doses of 0.6 to 6.5 mg/kg/d for 14 days in combination with dacarbazine 800-1,000 mg/m^2 per cycle.[9] Subsequently, G3139 was administered at doses of 5-9 mg/kg/d for 5 days in combination with dacarbazine 1,000 mg/m^2 per cycle.[10] The maximum tolerated dose of G3139 was 9 mg/kg/d administered by continuous IV infusion 5 days. In the 14-day schedule, toxicities were generally mild to moderate; however, 4 patients experienced grade 3 transaminase elevations and 5 patients had grade 3 lymphopenia. On the 5-day schedule, transient transaminase elevations occurred but were not dose-limiting. Laboratory studies demonstrated Bcl-2 downregulation and increased apoptosis after treatment.[10] Preliminary responses were encouraging, including several complete and partial responses, with demonstrated overall survival benefit.

G3139 and Irinotecan

The combination of G3139 and irinotecan has been evaluated in 19 patients with metastatic colorectal cancer (see Table 1, page 14).[11] G3139 was administered by continuous infusion on days 1-8 at doses of 3-7 mg/kg/d. Irinotecan was administered at doses of 280-350 mg/m^2 on day 6. Grade 3/4 diarrhea, grade 3 nausea and vomiting, and grade 4 neutropenia were dose-limiting with G3139 at a dose of 5 mg/kg/d in combination with irinotecan 350 mg/m^2. Laboratory studies confirmed Bcl-2 decreased protein expression in peripheral blood mononuclear cells. Among 9 patients previously untreated with irinotecan, there were 1 partial response and 2 patients with stable disease. Stable disease was also noted in 1 patient who had received prior irinotecan therapy.

G3139 and Paclitaxel

The combination of G3139 and paclitaxel has been evaluated in a phase I/II trial in patients with refractory small-cell lung cancer (SCLC) (see Table 1, page 14).[12] G3139 was administered by continuous infusion on days 1-8 at a dose of 3 mg/kg/d with paclitaxel 175 mg/m^2 on day 6. Dose-limiting hematologic toxicities were encountered in 2 of the first 3 patients treated, resulting in a dose decrease of paclitaxel to 150 mg/m^2 in subsequent patients. One patient developed a pruritic rash following therapy with G3139 and was removed from study; otherwise no toxicities greater than grade 2 were encountered. No objective responses were seen, although 2 of 12 patients (17%) achieved disease stabilization. At doses of G3139 of 3 mg/kg/d x 7 with paclitaxel 150 mg/m^2, treatment with the combination was considered tolerable.

Conclusions

Data from early clinical trials with G3139 indicate that therapy with this antisense oligonucleotide alone or in combination with chemotherapy is feasible, and early indications of efficacy are encouraging. The majority of systemic toxicities related to G3139 have been mild to moderate. However, the frequency of hepatic transaminase elevations in early trials using prolonged continuous infusions of G3139 was of some concern. With shortened G3139 infusion schedules, transaminase elevations appear to occur infrequently. Correlative laboratory studies have suggested adequate serum concentrations of G3139 can be achieved at clinically tolerable doses to effectively decrease Bcl-2 protein expression.

Preliminary data from several studies administering G3139 in combination with various chemotherapeutic agents, including docetaxel, dacarbazine, irinotecan, and paclitaxel, indicate that G3139 can be safely combined with chemotherapy. Preliminary reports of efficacy from these trials support the continued development of G3139 in several solid tumor types. Studies designed to determine the optimal dose and schedule of G3139 in combination with various chemotherapeutic agents are ongoing (see Table 2, page 15). Subsequent studies are planned to determine whether these combinations are superior to chemotherapy alone.

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